IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Theresa O'Keefe et al.	Art Unit	: 1643
Serial No.	: 10/733,563	Examiner	: David Blanchard
Filed	: December 10, 2003	Conf. No.	: 9540
Title	: HUMANIZED ANTI-CCR2 ANTIBODIES AND METHODS OF USE THEREFOR		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR 1.132 OF THERESA O'KEEFE, PH.D.

I, Theresa O'Keefe., pursuant to 37 C.F.R. § 1.132, declare the following:

1. I was employed by Millennium Pharmaceuticals, Inc. as a Consultant at the time the present application was filed. I am also an inventor on the above-referenced application. My Curriculum Vitae is attached.

2. I have read the office action dated July 21, 2006 and understand that the Examiner is rejecting the claims as being anticipated by Horvath et al., PCT Publication No.: WO 01/70266, and Horvath et al., U.S. Patent No.: 6,663,863. I also understand that the Examiner is rejecting the claims as obvious in view of LaRosa et al., PCT Publication No.: WO 01/57226, or Hancock et al., U.S. Publication No.: 2002/0042370, in view of Bonnefoy et al., PCT Publication No.: 99/58679. I have reviewed all of these references.

3. With regard to both of the Horvath references, the office action alleges that "the modified human IgG1 constant region comprising two mutations ($Leu^{235} \rightarrow Ala^{235}$ and $Gly^{237} \rightarrow Ala^{237}$)" of the cited references "is identical to SEQ ID NO:110" of the instant claims.

4. I disagree with this statement. There are several different amino acid sequences for human IgG1 in nature. Neither of the Horvath references cited by the Examiner provide an actual amino acid sequence for any human IgG1 constant region much less the specific amino acid sequence of SEQ ID NO:110.

5. The only disclosure of IgG1 constant regions in either of the Horvath references generally states that "antibodies...can comprise a constant region ... derived

from the κ or λ light chains,and/or the γ(e.g., γ1, γ2, γ3, γ4), μ, α (e.g., α1, α2), δ or ε heavy chains of human antibodies, including allelic variants. A particular constant region (e.g., IgG1), variant or portions thereof can be selected in order to tailor effector function." The only other discussion of constant regions in either of the Horvath references is specific to anti-CD18 antibodies, not anti-CCR2 antibodies, and again does not refer to a specific IgG1 amino acid sequence. The cited paragraph can be found,e.g., at page 25 of the Horvath PCT Publication which states

> Preferred ***anti-CD18 antibodies*** for administration to humans include humanized YFC%1.1 antibodies ... such as LDP-01 (humanized YFC51.1 which comprises a human γ1 heavy chain constant region having two mutations ($Leu^{235} \rightarrow Ala^{235}$ and $Gly^{237} \rightarrow Ala^{237}$) which reduce binding to Fcγ receptors. (***emphasis added***).

6. The arguments made in the office action incorrectly characterize the term "human IgG1 constant region" as referring to only one amino acid sequence. In fact, there are several different allotypes of human IgG1 constant regions in nature and their utilization varies among humans of different racial heritage. Therefore, this term does not necessarily suggest a particular amino acid sequence but instead refers to many different human IgG1 allotypes. For example, as early as 1985, it was known that there were at least 5 different allotypes for human IgG1 constant regions, namely Glm(a),Glm(f), Glm(z), nGlm(z) and Glm(x). Nothing in either of the Horvath references suggest one particular human IgG1 sequence over another. Therefore, the human IgG1 constant region generic disclosure in the Horvath references is not identical to the specific amino acid sequence provided in SEQ ID NO:110 of the claims.

7. In addition, as evidenced by the disclosure of both the Horvath references, there were several known mutations that could be made to a constant region to tailor effector function. With regards to anti-CCR2 antibody constant regions, neither of the Horvath references suggest a preference for the particular mutations made to the IgG1 sequence covered by SEQ ID NO:110. Instead, the Horvath references provide a list of several different approaches that can be taken. Thus, neither of the Horvath references suggest the particular allotype of a human IgG1 nor do they suggest a preference for the particular mutations chosen to arrive at the constant region covered by SEQ ID NO:110.

9. With regards to the obviousness rejection, the Hancock et al. publication and the LaRosa et al. publication have a similar disclosure to the Horvath et al. references discussed above. Neither the Hancock nor the LaRosa publications disclose a preference for a heavy chain constant region of a particular isotype. Neither of these publications disclose any human IgG1 heavy chain amino acid sequence. Moreover, neither of these publications disclose a preference for the particular mutations made to the IgG1 sequence covered by SEQ ID NO:110.

10. The Bonnefoy reference is cited in the Office Action as providing the "motivation to use the modified human IgG1 constant region" for the humanized CCR2 specific immunoglobulins of the claims. Specifically, the Office Action states that "one of ordinary skill in the art would have been motivated to use the modified human IgG1 constant region of Bonnefoy in the humanized CCR2 antibody ... since it lacks cytotoxicity and hence, would be less immunogenic in human patients."

11. I disagree with these arguments. The constant region appropriate for a particular antibody depends in part on the desired function of that antibody. For example, Bonnefoy et al. disclose various heavy chain constant regions that can be selected depending on whether a cytotoxic or non-cytotoxic form of the antibody is desired. Furthermore, even if a non-cytotoxic form of the antibody is desired, there were many different approaches known in the art at the time of filing for reducing cytoxicity of an antibody. For example, U.S. Patent No.: 6,682,736 discloses the use of a human IgG2 or human IgG4 constant region to produce anti-CTLA-4 antibodies that do not fix complement and PCT Publication Numbers WO 89/07142 and WO 94/29351 disclose several different positions that can be mutated in a human IgG1 constant region to reduce complement fixation. Furthermore, as discussed above, even if a human IgG1 heavy chain constant region was chosen, there were several different human IgG1 allotypes known at the time the present application was filed.

12. The disclosure of Bonnefoy et al. is for a completely different antibody to a completely different target than the claimed immunoglobulins. The disclosure of a heavy chain constant region of one antibody does not suggest that the particular constant region should be selected for the heavy chain constant region of a completely different antibody.

As discussed above, many different heavy chain constant regions were known in the art at the time of filing and nothing in any of the Hancock et al. publication, the LaRosa et al. publication or the Bonnefoy et al. publication teach or suggest that the particular heavy chain sequence recited in the claims should be selected for a humanized anti-CCR2 antibody.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: 1/5/07

Theresa O'Keefe, Ph.D.

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THERESA L. O'KEEFE, PH.D.

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SUMMARY

Senior Scientist with extensive experience managing people and projects in the development of immune based drugs from Discovery through early Development.

EXPERIENCE

SOLUTIA INC., St. Louis, MO — Present

Consultant, *Division of Entrepreneurial Growth*

- Developing methods to reduce contamination in biofuel production.
- Arranging outsourcing of method development and scale-up processes.

TETHYS RESEARCH LLC., Bangor, ME — Present

Consultant

- Development of research program for the modulation of common environmental allergens.

CRITICAL THERAPEUTICS INC., Lexington, MA — 2002-2006

Senior Scientist, *Molecular Immunology*

- Drug development areas included sepsis, rheumatoid arthritis and asthma.
- Supervised construction and equipping of original and expansion labs and tissue cultures.
- Developed strategy to adapt and optimize in-licensed targets.
- Designed and supervised creation of antigens and biotherapeutics for multiple programs in the areas of asthma, systemic inflammation and sepsis. This included moderate scale recombinant protein production in mammalian, bacterial and cell-free systems.
- Designed new in vitro assays for small molecule discovery and hit-to-lead optimization.
- Responsible for all molecular biology activities for discovery and preclinical programs and advised on future surrogate marker assays in clinical programs.
- Supervised genetic analysis of in vitro assays and assisted in the development of both in vivo and in vitro method of action models.
- Developed original technology xMAP RNA Profiling – a method to determine absolute concentrations of expressed RNA (femtograms/cell). Involved in out-licensing discussions with Invitrogen and BioRad.
- Chairman of Bio-safety Committee and Assistant Chairman of Institutional Animal Care and Use Committee.

MILLENNIUM PHARMACEUTICAL, INC., Cambridge MA — 1998-Present

Consultant, *Legal Department* (2003-Present)

- Advise Millennium on content and structure of therapeutics antibody patent applications and assist in the filing of new patents.
- Advise on the progression of therapeutic antibodies through preclinical and clinical development.

Senior Scientist I, *Department of Antibody Technologies* (2000-2002)

- Therapeutic areas included rheumatoid arthritis, multiple sclerosis, reperfusion injuries, prostate, ovarian, colon and breast cancer, biomarker development.
- Managed combined Antibody Engineering and Reagent Hybridoma Groups (15 people) that were responsible for the development of difficult engineered antigens, creation of hybridomas for the Inflammation, Metabolic Disease and Predictive Medicine programs and the creation of therapeutic antibodies and biologics. One product, MLNM1202, is currently in Phase II clinical trials.
- Created methods to produce intrinsically toxic proteins as both soluble and surface bound antigens. This allowed

the advancement of 5 stagnated oncology targets that are now projected to enter the clinic in between 2006 - 2008.
- Evaluated new external technologies to improve the development of biotherapeutics.

Scientist II, *Department of Biotherapeutic Pharmacology* (2000)
- Created system of expression vectors that allow rapid creation of multiple therapeutic, surrogate and clinical reagent antibodies. The vectors are for both research and manufacture with final production rates predicted to be greater than 1 mg / ml.
- Developed methods to greatly reduce humanization timeline and improve the conversion of phage display antibodies into stable biotherapeutics.
- Created novel antibody based forms of biotherapeutics with novel effector functions.

LEUKOSITE INC, (acquired by Millennium in 2000), Cambridge, MA 1998-1999

Senior Scientist, *Department of Immunobiology*
- Created the Antibody Engineering group.
- Created proprietary expression vector utilizing a very high expression system for the manufacture of antibodies.
- Humanized therapeutic antibodies.
- Assisted in final review of CAMPATH Biologic License Agreement (BLA).

PATENTS

HUMANIZED ANTI-CCR2 ANTIBODIES AND METHODS OF USE THEREFOR
U.S. Patent No. US 6,696,550; Issued Feb 24, 2004
Inventors: Gregory J. LaRosa, Christopher J. Horvath, Walter Newman, S. Tarran Jones, Siobhan H. O'Brien and Theresa O'Keefe.

IMMUNOGLOBULIN DNA CASSETTE MOLECULES, MONOBODY CONSTRUCTS, METHODS OF PRODUCTIONS AND METHODS OF USE THEREFOR
U.S. Patent No. 7,053,202, Issued May 30, 2006
Inventors: Theresa L. O'Keefe and Paul D. Ponath

HUMANIZED ANTI-CCR2 ANTIBODIES AND METHODS OF USE THEREFOR
International application no: PCT/US01/03537; published 09-Aug-2001
Inventors: Gregory J. LaRosa, Christopher J. Horvath, Walter Newman, S. Tarran Jones, Siobhan H. O'Brien and Theresa O'Keefe.

TANGO 197 AND TANGO 216 COMPOSITIONS AND METHODS
U.S. Application No. 2003144193, Filed December 20, 2001
Inventors: James B. Rottman, Theresa L. O'Keefe, Engin Ozkaynak, Judith J. Healey

HYBRID ANTIBODIES AND USES THEREOF
U.S. Application No. 20020147312, Filed January 30, 2002
Inventors: Theresa L. O'Keefe, Patrica Rao

HUMANIZED IMMUNOGLOBIN REACTIVE WITH □4□7 INTEGRIN
U.S. Provisional Application No. 60/737,582, Filed January 9, 2006

USE OF HMGB FRAGMENTS AND ANTI-INFLAMMATORY AGENTS
U.S. Application No. 20040141948, Filed November 20, 2003
Inventors: Theresa L. O'Keefe

HUMANIZED ANTI-CCR2 ANTIBODIES AND METHODS OF USE THEREFOR
U.S. Application No. 10/733,563, Filed December 10, 2003
Inventors: Theresa L. O'Keefe and Paul D. Ponath

RAGE PROTEIN DERIVATIVES
U.S. Application No. 20060057679, Filed July 20, 2004
Inventors: Theresa L. O'Keefe, Peter Luciano and Shixin Qin

MONOCLONAL ANTIBODIES AGAINST HMGB1
U.S. Application No. 20050152903, Filed September 10, 2004
Inventors: Walter Newman, Shixin Qin, Theresa L. O'Keefe and Robert R. Obar

NOVEL POLYADENYLATION SEQUENCE FOR MAMMALIAN EXPRESSION VECTORS
U.S. Application No. 60/589,679, Filed July 20, 2004
Inventor: Theresa L.O'Keefe

EDUCATION

HARVARD EXTENSION SCHOOL, HARVARD UNIVERSITY, Cambridge, MA
Project Management, January 2007

TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT, TUFTS UNIVERSITY, Boston, MA
Postgraduate Course in Clinical Pharmacology, Drug Development and Regulation, February 2004

SACKLER SCHOOL OF BIOMEDICAL SCIENCES, TUFTS UNIVERSITY, Boston, MA
Ph.D., Immunology, December 1991
Thesis: Molecular Analysis of Pathogenic Anti-DNA Autoantibodies from the Lupus Prone (SWR x NZB)F_1 Mouse.
Advisor: Dr T. Imanishi-Kari.

PURDUE UNIVERSITY, West Lafayette, IN
M.S., Veterinary Physiology, August 1986
Thesis: Prostacyclin and Thromboxane Production by Porcine Vascular Endothelial Cells and White Blood Cells in Response to Endotoxin. Advisor: Dr. G.D. Bottoms.

MOUNT HOLYOKE COLLEGE, South Hadley, MA
A.B., Biochemistry and Biological Sciences, May 1984
Honors Thesis: Prevention of Cataracts in Pink-eyed RCS Rats by Dark-rearing and the Influx of Macrophages into the Cortex of the Vitreous. Advisors: Dr. J. Townsend (MHC) and Dr. H.H. Hess (NEI). Project performed in conjunction with the National Eye Inst., NIH, Bethesda, MD

PUBLICATIONS

1. Hess, H.H., J.S. Zigler Jr., T.L. O'Keefe and J.J. Knapka, 1987. Environmental Factors in Cataractogenesis in RCS Rats in **The Microenvironment and Vision**. J.B.Sheffield, and S.R. Hilfer, Eds. New York, Berlin, Springer-Verlag, pp 169 - 194.

2. O'Keefe, T.L., S. Bandyopadhyay, S.K. Datta, and T. Imanishi-Kari. 1990. Variable Region Sequences of an Idiotypically Connected Family of Pathogenic Anti-DNA Auto-antibodies. **J. Immunol. 144**: 4275.

3. O'Keefe, T.L., H.H. Hess, J.S. Zigler Jr., T. Kuwabara and J.J. Knapka. 1990. Prevention of Cataracts in Pink-Eyed RCS Rats by Dark Rearing: Significance for the Hypothesis of Singlet Oxygen Generation by Light and Retinaldehyde in Vivo. **Exp. Eye Res. 51**: 509.

4. Ghatak, S., T.L. O'Keefe, T. Imanishi-Kari and S.K. Datta. 1990. Selective Strain Distribution Pattern of a Germline VH Gene for a Pathogenic Anti-DNA Autoantibody Family. **International Immunol. 2**: 1003.

5. Hess, H.H., T.L. O'Keefe, T. Kuwabara, and I.V. Westney. 1991. Numbers of Cortical Vitreous Cells and Onset of Cataracts in RCS Rats. **Invest. Ophthalmol. Vis Sci. 32**: 196.

6. Datta, S.K., S. Rajagapalan, T.L. O'Keefe, S. Ghatak and T. Imanishi-Kari. 1991. Pathogenic Anti-DNA Autoantibodies and Pathogenic Autoantibody-Inducing T cells. in **Molecular Immunobiology of Self-Reactivity**. C.A. Bona and A.K. Kanshik, Eds. New York. Marcel and Dekker Inc. pp 133 - 153.

7. O'Keefe, T.L., S.K. Datta, T. Imanishi-Kari. 1992. Pathogenic Anti-DNA Auto-antibodies in Lupus Mice Arise From Cationic Mutations of a Germline Gene that Belongs to a Large VH Gene Sub-family. **Eur J. Immunol. 22:** 619.

8. Zhang, L., R.R. French, H.T. Chan, T.L. O'Keefe, M.S. Cragg, M.J. Power, and M.J. Glennie. 1995. The Development of Anti-CD79 Antibodies for treatment of B-cell neoplastic disease.. **Thera. Immunol. 2**: 191.

9. O'Keefe, T.L., G.T. Williams, S.L. Davies and M.S. Neuberger. 1996. Hyper-responsive B cells in CD22-deficient mice. **Science 274:** 798.

10. O'Keefe, T.L., G.T. Williams, S.L. Davies and M.S. Neuberger. 1998. Mice carrying a CD20 gene disruption. **Immunogenetics 48**: 125.

11. Ehrenstein, M.R., T.L. O'Keefe, S.L. Davies and M.S. Neuberger. 1998. Targeted gene disruption reveals a role for secretory IgM in accelerating the maturation of the primary immune response. **PNAS 95**:10089.

12. O'Keefe, T.L., G.T. Williams, F. D. Batista and M.S. Neuberger. 1999. Deficiency in CD22, a B Cell-specific Inhibitory Receptor, Is Sufficient to Predispose to Development of High Affinity Autoantibodies. **J. Exp Med 189:** 1307.

13. Mary, C., C. Laporte, D. Parzy, M-L. Santiago, F. Stefani, F. Lajaunias, R.M.E. Parkhouse, T.L. O'Keefe, M.S. Neuberger, S. Izui and L. Reininger. 2000. Dysregulated Expression of the Cd22 Gene as a Result of SINE Insertion in Cd22a Lupus-prone Mice. **J. Immunol 165:** 2987.

14. Fehr, T., C. Lopez-Macias, B. Odermatt, R.M. Torres, D.B. Shubarth, T.L. O'Keefe, P. Matthias, H. Hengartner and R.M. Zinkernagel. 2000. Correlation of anti-viral B cell responses and splenic morphology with expression of B cell-specific molecules. **International Immunol. 19:** 1275.

15. Ozkaynak E, L. Wang, A. Goodearl, K. McDonald, S. Qin, T. O'Keefe, T. Duong, T. Smith, J.C. Gutierrez-Ramos, J.B. Rottman, A.J. Coyle, W.W. Hancock. 2002. Programmed death-1 targeting can promote allograft survival. **J. Immunol. 169:**6546-53

RESEARCH GRANTS

RHE/97/275/G The Role of CD22 in the Development of Systemic Autoimmunity, Nuffield Foundation, Oliver Bird Fund for Research into Rheumatism, 1 Sept 1997 - 31 Aug 1999; £51,724 for direct cost over two years

FELLOWSHIPS

Human Frontiers Science Project Organization Fellowship, June 1992 - May 1994
Also awarded but declined the European Molecular Biology Organization Long Term Fellowship (for June 1992 - May 1993) and the Arthritis Foundation Fellowship (for June 1992 - May 1995)

ADDITIONAL RESEARCH EXPERIENCE

Oliver Bird Fellow (US equivalent – Assoc. Prof.), September 1997 - September 1998;
Scientific Fellow (supported by Howard Hughs), June 1994 - August 1997;
Visiting Scholar, HFSPO Fellow, June 1992 - May 1994
Medical Research Council Laboratory of Molecular Biology, Cambridge, U.K.
Laboratory of Dr. Michael Neuberger. Worked with the laboratories of Drs. Cesar Milstein, Greg Winter and Max Perutz

Postdoctoral Fellow, January 1992 - May 1992
Department of Pathology, Tufts Univ. School of Medicine, Boston, MA; Laboratory of Dr. Syamal K. Datta

Graduate Student, September 1986 - December 1991
Graduate Program in Immunology, Tufts University Sackler School of Biomedical Sciences, Boston, MA; Laboratory of Dr. Thereza Imanishi-Kari

Graduate Student, September 1984 - August 1986
Department of Veterinary Physiology and Pharmacology, Purdue University, West Lafayette, IN; Laboratory of Dr. Gerald D. Bottoms

Independent Undergraduate Research Project, September 1983 - April 1984
Department of Biological Sciences, Mount Holyoke College, South Hadley, MA
Advisors: Dr. Jane Townsend (MHC) and Dr. Helen H. Hess (NEI)
Research supported by the National Eye Institute, NIH

Research Associate, June - August 1983 and June - August 1984
National Eye Institute, NIH, Bethesda, MD; Laboratory of Dr. Helen H. Hess

TEACHING EXPERIENCE

Scientific Advisor-Rubrics Development Team, Northeastern Univ., Boston, MA 2004-2005
Appointed to National Science Foundation supported program to create a web based system to capture the development of students' academic progress in the Dept of Biology. Part of the remit is to determine academic training necessary for an advance 21st century education.

Advisor for Co-op Program at Critical Therapeutics Inc, 2002-2006
Supervise both scientists and students participating in CRTX's student training program

Senior Advisor for Biology Co-op Program at Millennium Pharmaceuticals, 1999-2002
Supervise both scientists and students participating in MLNM's student training program

Teaching Assistant, 1987-1989; Tufts University
Led discussion groups for Veterinary and Graduate students as part of a general lecture course in Immunology

Teaching Assistant, September 1984 - May 1986; Purdue University
Assisted in laboratory course in Veterinary Physiology for Veterinary students

Teaching Assistant, September 1981 - May 1984; Mount Holyoke College
Assisted in laboratory sections of General and Organic Chemistry courses for undergraduates